The Inflamed Bowel

Introduction

This lesson is about diseases involving inflammation of the colon. Diverticulitis and appendicitis are **acute, infectious** causes of colonic inflammation and are treated with antibiotics and surgery. Ulcerative colitis, Crohn's disease, and microscopic colitis are **chronic autoimmune** causes of intestinal inflammation and are treated with anti-inflammatory medications (and sometimes surgery).

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is often ulcerative colitis (UC) or Crohn's disease (colloquially, Crohn's). There is a third consideration, microscopic colitis, though the presentation and severity of the disease are dwarfed by the more common and dichotomous UC and Crohn's. Do not learn IBD as UC vs. Crohn's, comparing them against one another. Learn them individually, then compare them.

The mechanisms of UC and Crohn's have far more overlap than we let on. The two presentations are extremely different from each other. We've separated the diseases based on the information you already know from Immunology in an attempt to link the histological findings to the pathogenesis, teaching them as separate diseases without overlap to ensure that you will recognize them as completely different diseases. Because although the underlying inflammation may have overlap, identifying a patient with one or the other is the skill you are going to put to work.

Ulcerative Colitis (UC)

UC causes ulcers (ulcerative) of the colon (colon-itis, colitis). Start with this, and much of the disease presentation and diagnostic findings will make sense. Ulcers are deep erosions through the mucosa and into the submucosa. Very rarely do they reach the muscularis externa. **Ulcers are not transmural** and, therefore, cannot cause perforations or fistulas. UC affects **only the colon,** and the affected colon is **continuous**, with an **abrupt change** at the affected-unaffected interchange. The lesions of UC always begin at the rectum, above the pectinate line, and ascend to however proximal the disease gets. The unaffected proximal colon will never develop disease, whereas the affected distal colon will have disease for the patient's life (or until resected). How proximal the affected colon is determines its severity and how it is named. Really bad UC can reach the cecum, called **pancolitis**. Not-so-bad UC can stop at the rectum, called **proctitis**. Most UC is a left-sided disease, called **colitis**, affecting the extent of the hindgut—from the rectum to the distal third of the colon.UC produces "large ulcers" wherever the colon is affected. "Large" means that they encompass a large surface area, and "ulcers" means that they do not penetrate very deep; therefore, these are termed **broad-based ulcers.** Instead of imagining multiple ulcers against a normal colonic mucosa, imagine that the entire mucosa and part of the submucosa are completely ulcerated. Now imagine islands of regenerating mucosa sporadically distributed throughout the rest of the affected colon. This creates a smooth affected colon with islands of mucosa "raised" above the affected areas. When an endoscopist performs a routine screening colonoscopy on a patient without UC, raised lesions off the flat mucosa are called polyps. When an endoscopist performs a colonoscopy on a patient with UC, there are "raised lesions" (regenerating mucosa) over a flat "mucosa" (affected area); therefore, the areas of regenerating mucosa appear to be polyps, and so are termed **pseudopolyps.** Pseudopolyps are healthy mucosa trying to regenerate against an inflamed ulcer (see Figure 14.4).

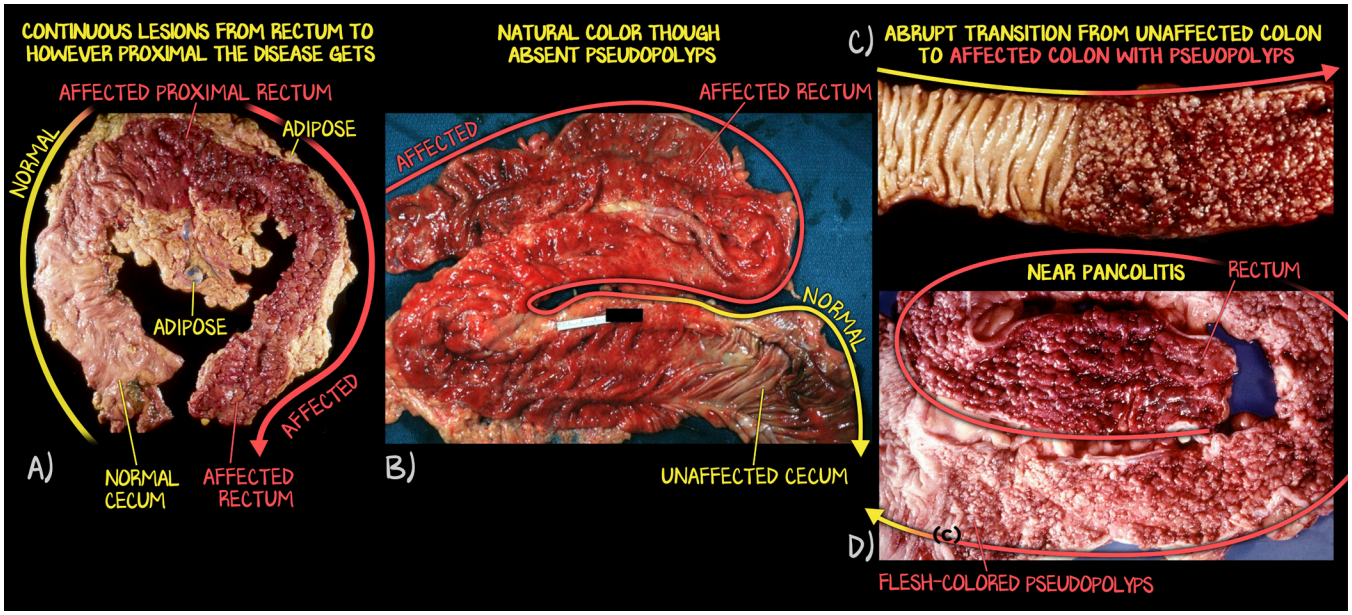

Figure 14.1: Ulcerative Colitis in Gross
(a) UC always involves the rectum. The lesions are continuous from the rectum to however proximal the disease gets. Seen here are inflamed mucosa without pseudopolyps (proximal transverse rectum) and inflamed mucosa with pseudopolyps (rectum). (b) Nearly pancolitis, this example shows no pseudopolyps but rather a hemorrhagic inflammation from the rectum to near the cecum. Notice how the lesions are continuous. (c) UC has an abrupt transition from the distal affected rectum to the proximal unaffected mucosa. (d) A particularly severe form of UC with pseudopolyps nearly to the appendix and active inflammation throughout.

UC is an autoimmune disease in which the inflammatory process is mediated by a **T_H17** response—**neutrophils** arrive. The neutrophils exit blood vessels in the lamina propria and enter the mucosa. They exit the blood vessels to enter the connective tissue of the lamina propria and the epithelium. In the colon, there are only crypts (invaginations of the simple columnar epithelium into its own lamina propria) and no villi (evaginations of the simple columnar epithelium and lamina propria into the lumen, above the surface epithelium). Thus, neutrophils migrate into the crypts. The presence of neutrophils in tissue is called an abscess. **Crypt abscesses** are a hallmark of UC histology. However, there is NO process of acute inflammation and wound healing—although there are neutrophils, there will be no macrophages and **no fibroblasts**—thus, fibrosis is rare and only superficial in the submucosa, where present. The ulcers **rarely get below the submucosa**. Granulomatous inflammation (multinucleated giant cells, which are revved-up macrophages, granulomas) is absent in UC. Neutrophils do not cause granulomas.

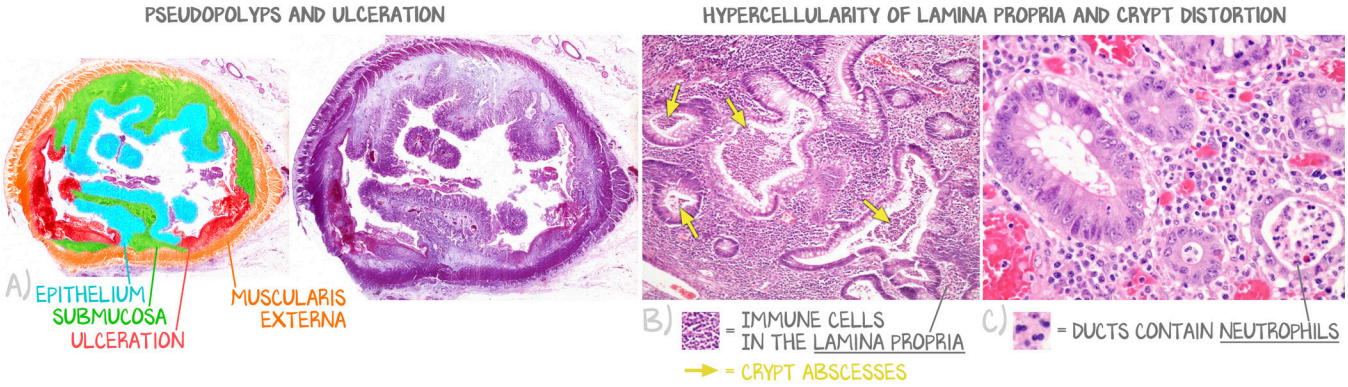

Figure 14.2: Ulcerative Colitis Histology
(a) Low-powered whole-mount histology of the colon demonstrating pseudopolyps, with the normal epithelium appearing as growths into the lumen rather than normal mucosa. The ulcerations are severe and deep, degrading the submucosa and almost reaching the muscularis externa. (b) Moderate-powered magnification demonstrating hypercellularity in the lamina propria, crypt distortion (this is not recognizable as colonic mucosa without context), and multiple crypt abscesses—neutrophils in the lumens of the crypts. (c) High-powered magnification of the colon showing increased vascularity (RBCs), hypercellularity of the lamina propria, and a crypt abscess, giving a clearer view of the elements seen in panel b.

Because there is **no transmural inflammation**, the adventitia is never involved, so fistulas and strictures cannot occur. Inflammation rarely reaches the muscularis externa when severe. Inflammation that far down can damage the myenteric plexus, leading to a loss of motor function and resulting in colonic dilation and **toxic megacolon**. To cause megacolon, the inflammation must be broad-based (UC usually is) and very deep (UC usually is not). Megacolon impairs the contraction of smooth muscle. Both the longitudinal contractility of the taeniae coli and the circular muscle lead to the loss of visible haustra in affected areas, called a **lead-pipe sign** on imaging. A lead-pipe colon is at risk for toxic megacolon. Very few patients with UC develop toxic megacolon, but it is possible.

The symptoms of UC are caused by friable, inflamed mucosa at the distal end of the GI tract. This means that most absorption has already occurred, so there will be no malabsorption issues. Because the inflammation is close to the rectum, and there is a lot of inflammation, UC presents with **bloody diarrhea** and **left lower quadrant pain**. Because so much of the colon is affected and the stem cells in the crypts are fighting a constant battle of regeneration against inflammation, the increased proliferation of colonic cells **increases the risk of colon cancer**. Patients with UC have such a high risk that they must start undergoing **colonoscopies 8 years after diagnosis** and then **every year** thereafter. Removing the diseased colon is curative. Prophylactic hemicolectomy is recommended for left-sided disease; colectomy for pancolitis carries morbidity that should be balanced with cancer risk and response to medical therapy.

Crohn's Disease

Learning UC before learning Crohn's helps deduce Crohn's because it is "the other one" and acts very unlike UC. Whatever UC has, Crohn's has the opposite.

Crohn's disease is characterized by **transmural inflammation** that can occur **anywhere in the GI tract**, is a **T_H1-mediated** autoimmune disease (recruits macrophages), and is characterized by **noncaseating granulomas** on histology (which macrophages make). Crohn's disease goes deep but not out. The lesions of Crohn's are described as **knife-like** in that thin slices of the mucosa are affected, but the affected areas can involve the serosa—slicing the intestine as with a scalpel from the lumen out. Because of this knifing, there is often a good amount of healthy mucosa between intervening affected areas, giving a **cobblestone appearance** on colonoscopy. Because the knife-like fissures go through the

mucosa, submucosa, muscularis externa, **and serosa**, there is a potential for **perforation**. If the knife-like fissures go through into another organ, **fistulas** can form. Fistulas can be to the skin, other sites on the intestines, or any other hollow organ. In cases with extensive transmural disease, mesenteric fat frequently extends around the serosal surface (creeping fat). Because the lesions can occur anywhere in the GI tract and are discontinuous (in comparison to UC's continuous lesions), Crohn's lesions are defined as **skip lesions**. Inflammation down to the adventitia and subsequent **fibrosis** (which is abundant in Crohn's) results in **strictures**. Strictures can be revealed on barium studies (upper GI series, barium enema) and will show the **string sign**.

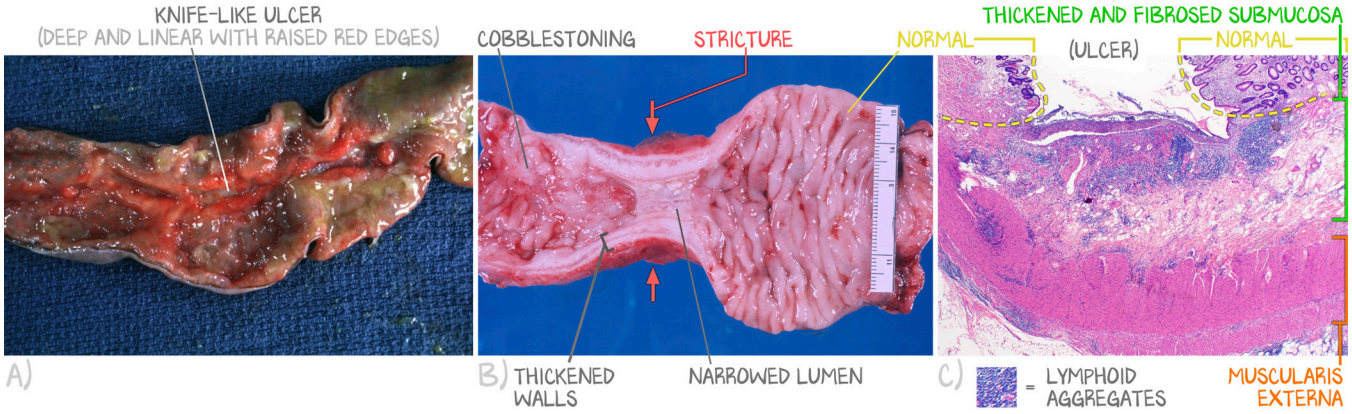

Figure 14.3: Pathologic Crohn's Disease.
(a) Section of small intestine showing the linear, knife-like ulcer that is both deep and long but not broad based. (b) Resected Crohn's enterocolitis specimen. Resection is usually performed in cases with severe complications, including obstruction from strictures, fistulas, bowel perforation, hemorrhage, and abscess formation. This patient developed intestinal obstruction due to stricture. The mucosa to the right of stricture is normal. The mucosa to the immediate left of the stricture shows some cobblestoning, beyond which is normal-appearing mucosa. The area of stricture appears thickened, firm, and pipe-like due to submucosal fibrosis. (c) Low-magnification view showing Crohn's enterocolitis. There is an aphthous ulcer (flattened area on the top) surrounded by intact but inflamed and distorted mucosa on either side. There is full-thickness inflammation extending through the submucosa and muscularis externa to the serosa (near the bottom of the image).

The terminal ileum is the most common location to find Crohn's lesions. Because Crohn's **can affect the small intestine** and **often involves the terminal ileum** (fat absorption, fat-soluble vitamin absorption), Crohn's **can cause malabsorption**. It usually presents as **copious watery diarrhea** resulting in significant weight loss. Extraintestinal manifestations are generally rheumatological—uveitis, enteropathic arthritis, ankylosing spondylitis, and the like. Due to their overlapping mechanisms, patients with Crohn's or UC have a higher association with PSC and colorectal cancer than those without these diseases. But we want you to keep these diseases polarized. Because there absolutely is an association between UC and PSC and colorectal cancer, learn that Crohn's "is NOT" associated with those diseases.

UC versus Crohn's

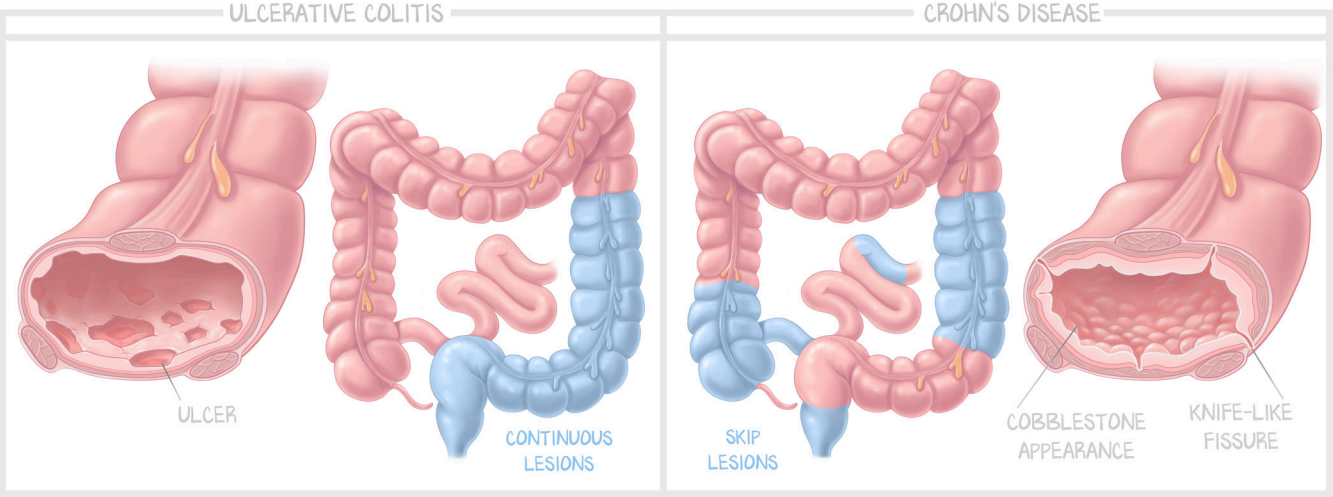

Figure 14.4: Crohn's vs. UC
Crohn's disease has transmural inflammation and knife-like fissures that occur anywhere in the GI tract. UC has superficial inflammation of the mucosa and pseudopolyps and occurs only in the colon.

UC is very clearly associated with primary sclerosing cholangitis (PSC). So much so that patients with UC receive routine screening for PSC with alkaline phosphatase and direct bilirubin tests (see Gastrointestinal: Hepatobiliary #3: *Cholestasis*). Surgery is not indicated for Crohn's and is **not curative**. Resections may be required due to perforation, obstruction (strictures), or fistulas. Crohn's flares are treated with **corticosteroids**. Long-term treatment of Crohn's is with **biologics,** such as the monoclonal antibodies **infliximab** or adalimumab (TNF-α inhibitors).

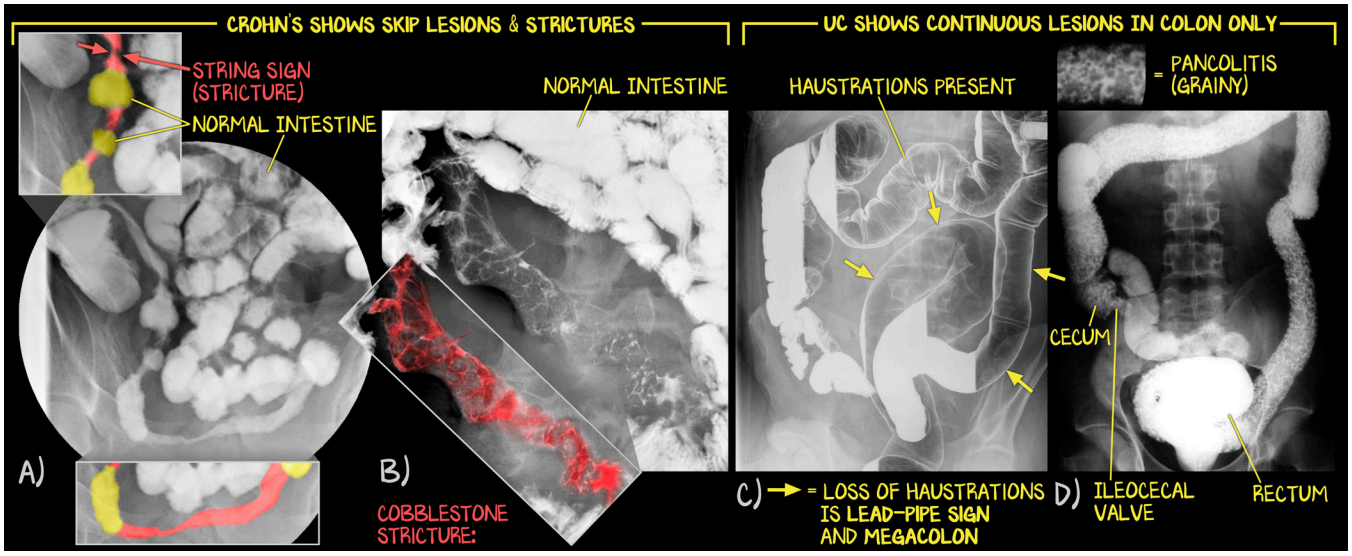

Figure 14.5: Radiological UC vs. Crohn's
(a) Barium study of a patient with active Crohn's disease showing mostly normal small intestine, except for the string-like strictures punctuated with normal intestine, demonstrating the skip lesions radiographically. (b) Cobblestoning can be detected on barium studies as well, as shown here. The lesion is flanked by normal intestine, indicating yet another skip lesion. (c) Barium enema demonstrating pancolitis, the irregular texture of the colon visible throughout. The ileocecal valve is affected and connected to the unaffected small intestine proximally. UC only affects the colon. (d) When severe, when inflammation affects the myenteric plexus of the distal colon, there is a lead-pipe sign caused by the absence of haustrations, indicative of toxic megacolon.

ULCERATIVE COLITIS	FEATURE	CROHN'S
Colon	**LOCATION IN BOWEL**	Anywhere in the GI tract
Mucosa only	**DEPTH OF INVASION**	Transmural
Diffuse, continuous	**DISTRIBUTION**	Skip lesions, discontinuous
Superficial, broad	**ULCERS**	Knife-like
T_H17 = Neutrophils	**MECHANISM**	T_H1 = Macrophages
Crypt abscesses	**HISTOLOGY**	Macrophages, granulomas
No	**FIBROSIS**	Yes
No	**STRICTURES**	Yes
No	**FISTULAS**	Yes
No	**MALABSORPTION**	Fat-soluble vitamins (ADEK)
Yes Yes Yes	**CANCER**	Only if colon
PSC	**EXTRAINTESTINAL**	Uveitis, arthritis
Yes	**MEGACOLON**	No
Curative	**SURGERY**	Only for fistulas and strictures

Table 14.1: Crohn's vs. UC
On your first readthrough, review UC only. After reading the section on Crohn's, return here and review Crohn's. Then compare them.

Microscopic Colitis

The discussion of inflammatory bowel disease often revolves around whether it is Crohn's or UC. What gets left out of the discussion is **microscopic colitis**. Microscopic—only visible on microscopy—colitis—colon inflammation. These patients have **normal-appearing colons** on visual inspection, but a biopsy reveals something very different. The patient will receive a biopsy because **chronic diarrhea** symptoms are refractory to treatment, serological work-up has been negative, and some GI finally gives her (women in middle age are most commonly affected) a colonoscopy. And despite the normal-appearing mucosa, that GI correctly samples the mucosa to reveal the microscopic diagnosis. These idiopathic diseases present with chronic, non-bloody, watery diarrhea without weight loss. Radiological and endoscopic studies are typically normal.

Microscopic colitis can be either collagenous or lymphocytic. **Collagenous colitis** has a deposition of collagen in the **subepithelial region**. It is within the layer of the mucosa but below the epithelial basement membrane and above the muscularis mucosae (so in the lamina propria). **Lymphocytic colitis** has many **lymphocytes** in the **intraepithelial layer**.

Diverticula

A true diverticulum is an extrusion of all three layers—mucosa, submucosa, and muscularis externa—beyond the plane of the normal bowel. A true diverticulum, such as Meckel's diverticulum, is often an anatomical defect. Diverticulosis of the colon is a false diverticulum—not all three layers extend past the plane of the bowel. Instead, at an area of weakened circularis (we'll get there in a second), there is an **acquired** outpouching of the mucosa and submucosa **through the circularis**. The colon is particularly vulnerable to developing these acquired diverticula because of the high pressure contracting against the hard stool. Even more vulnerable are the areas of the colon where the vascular supply penetrates the circular muscle. The longitudinal muscle layer of the colon—the taeniae coli—doesn't wrap all the way around the colon the way the longitudinal muscle layer does in the intestine. That means there is only a thin film of longitudinal muscle protecting the myenteric plexus, and the responsibility of resisting luminal pressures lies with the circular smooth muscle—the circularis. Because the blood vessels come from outside the bowel towards the lumen, where the vasa recta penetrate the circularis, they inherently must interrupt the smooth muscles. There, at the vasa recta penetration site, there is neither circular nor longitudinal muscle. Through this weakness, the mucosa and submucosa go. Diverticulosis has been established. From here, they will never return to normal, complicated by hemorrhage and obstruction.

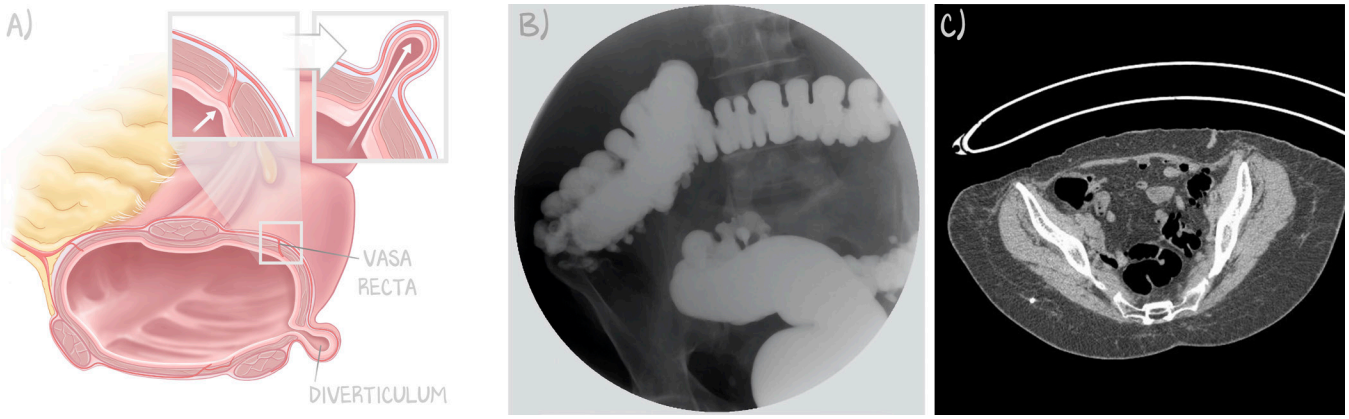

Figure 14.6: Diverticular Disease
(a) A schematic of how diverticulosis can form at regions of weakened circularis. Schematic of the diverticulum, the false lumen, and the weak point at the site of the vasa recta. (b) Barium enema showing the outpouchings from the lumen of the colon. (c) CT showing acute diverticulitis with thickened bowel wall and inflammation of the mesentery atop.

Diverticulosis is the condition of having diverticula. It is asymptomatic. It occurs in patients over 40 years of age. There is nothing to be done for diverticulosis except to decrease the risk of more diverticula forming and prevent complications. High-fiber diets lead to good bowel hygiene. Having soft, well-formed stool that passes with ease is the goal to prevent more diverticula. The avoidance of nuts and seeds is a critical lifestyle intervention to prevent complications. These foods contain undigestible matter and can easily block a diverticulum. Nuts and seeds are considered extremely healthy sources of proteins and fats but must be avoided in patients with diverticulosis. Most diverticulosis goes unnoticed by the patient until it is found on routine colonoscopy (e.g., for cancer screening).

Diverticular hemorrhage is the most common cause of lower GI bleeding in patients over 40. The diverticula form where the wall is weakest—where the vasa recta penetrate. If the diverticulum gets stretched too far, it can cause the vessel to bleed. These are small vessels and so close off quickly. The patient will present with hematochezia—bright red blood per rectum. Although the patient's stool is visually impressive, the symptoms are otherwise mild. There is insufficient blood loss to provoke hemodynamic derangement. The problem with hematochezia is that, upon presentation, it isn't possible

to tell whether it is from a self-limiting diverticular hemorrhage or a life-threatening hemorrhage. (There are reassuring features, but that subject is for Clinical Sciences.) But if the bleed has already self-limited (the bleeding has stopped) and there has been no change in hemoglobin level or hemodynamics, especially in a patient known to have diverticulosis, this suggests diverticular hemorrhage. In this case, no investigation needs to be pursued. If the diagnosis were not already established, a colonoscopy would reveal the diverticula (usually there is more than one).

Diverticulitis. If that seed, undigested food, or just a fecalith (feces stone) blocks off one of these diverticula, because bacteria are all over the colon, the bacteria that it traps in the diverticulum can fester. Bacterial growth causes inflammation of the diverticula, called diverticula-itis. Diverticulitis is "left-sided appendicitis." The patient will present with **left lower quadrant** abdominal pain, **fever**, **leukocytosis**, and vomiting. A contrast CT of the abdomen will reveal the diverticula and surrounding inflammation. Treatment depends on the severity. Microperforations and small abscess formation are treated with **gram-negative and anaerobic coverage** (ciprofloxacin + metronidazole). Worsening abscess or frank perforation is a surgical emergency. **Never perform a colonoscopy on diverticulitis**—the inflamed wall is at high risk for frank perforation when air is insufflated during the procedure. If the diagnosis of diverticulosis is not already established, get a colonoscopy 2–6 weeks after the infection has cooled off to rule out cancer and confirm the diverticulosis. Because the inflammation is already outside the muscularis externa, inflammation may get up against the serosa of a nearby organ, causing fistulas.

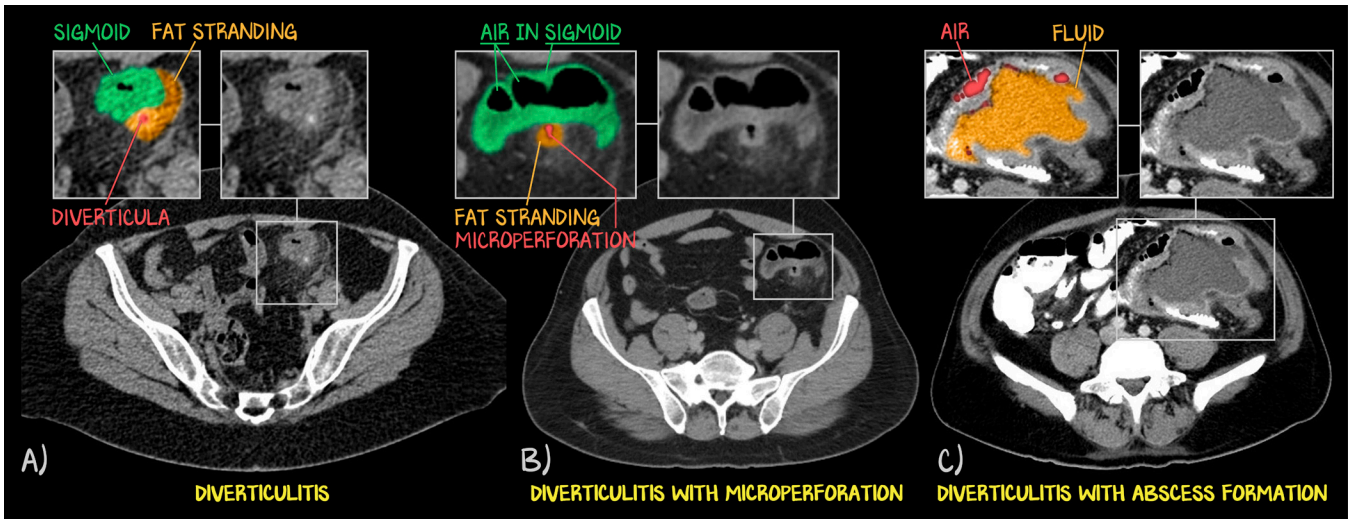

Figure 14.7: Diverticulitis Spectrum
(a) Axial abdominal CT showing a small diverticulum outpouching from the sigmoid colon with adjacent fat stranding. Fat stranding is where the surrounding fatty tissues are lighter/grayer (increased attenuation) due to an increase in fluid (edema) and is seen with inflammatory changes, such as in this patient with diverticulitis. (b) Diverticulitis with a microperforation and small abscess; image shows a small diverticular outpouching of the sigmoid-colic junction with surrounding fat stranding (red). (c) The diverticulum is two slides below the slide shown, though this section demonstrates a large collection of extraintestinal fluid with pockets of air, indicating a large abscess.

Appendicitis

The appendix is a vestigial organ. We don't need it. But boy, does it cause trouble. If a **fecalith** (adults) or **lymphoid hyperplasia** after a viral diarrheal illness (children) blocks the appendix, there is a long winding tunnel that can grow a pretty large colony of bacteria. And because it is vestigial, it is hidden away from the normal flow of stool. That means the immune system and the patient don't recognize

the bacteria are developing until it gets pretty bad. As the bacteria grow, the appendix distends. Rising intraluminal pressure can lead to vascular compromise, ischemia, and necrosis. If there are bowel distention and necrosis, they will ultimately lead to perforation. Perforation of a bacteria-and-pus-filled bag into the peritoneal cavity is very bad and very hard to clean out. Better to catch it before the appendix ruptures, surgically removing a nicely contained bag of bugs.

The presentation of appendicitis is so classic that a CT need not be done (although it is often done to confirm). The patient will experience **periumbilical pain** that eventually **migrates to the right lower quadrant**. McBurney's point is one-third the distance from the umbilicus to the right anterior superior iliac spine, about the location of the cecum. This is the site where the pain will have migrated to. The patient will present with **fever**, **nausea**, and **anorexia**. There are often local peritoneal signs, if not an acute florid abdomen, exhibiting **involuntary guarding** and **rebound tenderness**.

Rebound tenderness should never be elicited by jabbing your hand into the affected area and pulling it away quickly. This is archaic and induces an extreme amount of pain. It is the mark of a novice, expecting the "rebound of the compressed abdomen" to yield a diagnostic clue for the presence of "rebound tenderness." The same diagnostic information can be obtained by percussing an unaffected area, an area without pain. If percussing the unaffected area elicits pain in the affected area, that is rebound tenderness, and the patient is peritoneal. Only do the poke-and-release technique when you need to show a surgeon that the patient should be in the operating room, and you are at the bedside together, him arguing that there are no signs of an acute abdomen. Never be that surgeon.

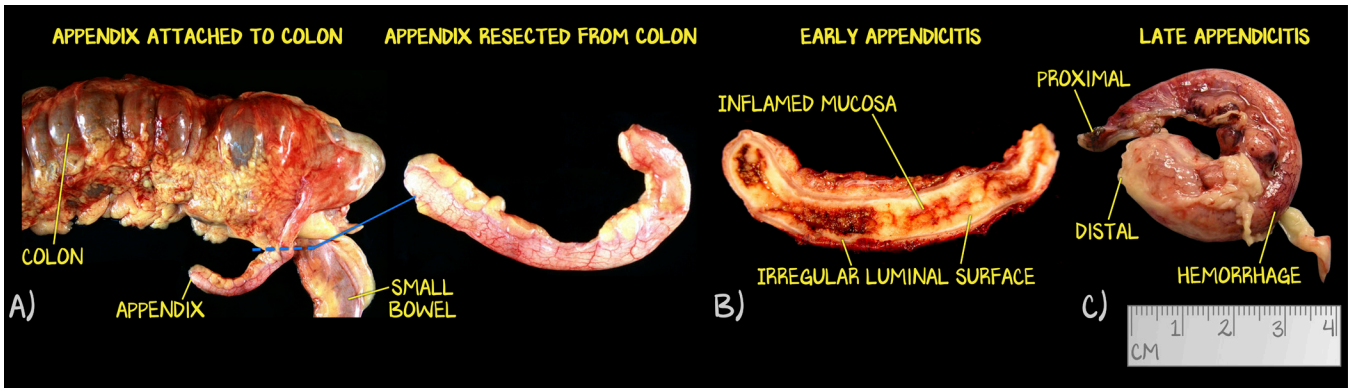

Figure 14.8: Pathologic Appendicitis
(a) Normal-appearing appendix coming off of a normal cecum leading to a normal colon. The terminal ileum can be seen at the bottom right. (b) Enlarged and sausage-like (botuliform) appendix. This longitudinal section shows the angry red, inflamed mucosa with its irregular luminal surface. Diagnosed and removed early in the course of the disease, this appendix does not show late complications, like transmural necrosis, perforation, and abscess formation. (c) Gross sample of a resected curved vermiform appendix with congestion of the serosal surface, hemorrhage, and fibrinous exudates in the most distal appendix.

Several maneuvers can assess for appendiceal inflammation. If the movement of nearby structures elicits pain, then the appendix could be inflamed. These maneuvers help differentiate the local peritonitis of the appendix from another inflammatory disease of the right colon. Other signs that can be elicited are the **psoas sign** (passive extension of the hip), **Rovsing's sign** (deep palpation of the LLQ leading to RLQ. . . which is a more brutal version of the rebound method described above; don't do this either), and **obturator sign** (passive internal rotation of a flexed hip elicits pain). Being positive is often ancillary and does not affect management.

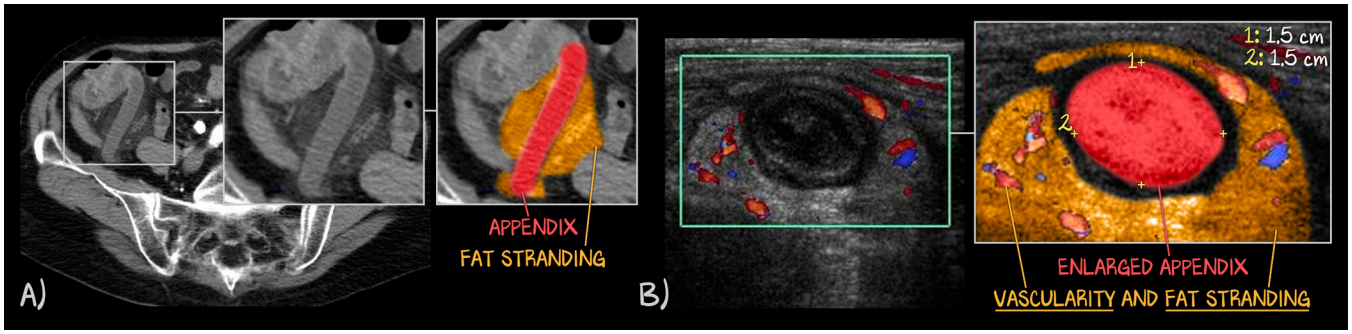

Figure 14.9: Radiographical Appendicitis
(a) Axial abdominal CT with IV contrast showing a retrocecal, distended appendix with mild fat stranding. It is greater than 6 cm and thus pathological. (c) Transverse ultrasound with color Doppler showing a thickened appendix that measures 1.1 cm (enlarged in the pediatric population). Color Doppler shows hyperemia of the fat around the appendix (mesoappendix).

A diagnosis can be made with **CT with contrast** to show the inflammation in the area of the appendix. This is the preferred method in adults and in those with significant adipose tissue (where an ultrasound would be difficult). An **ultrasound** can make the diagnosis as well and is the preferred method to diagnose someone who should not be exposed to radiation—children and pregnant women. The patient will be septic. Treat the sepsis with intravenous fluids and antibiotics (gram-negative and anaerobic coverage). The definitive treatment is **surgery**. However, CODA demonstrated that antibiotic treatment may not be inferior to surgical management for some patients early in the disease course and without any complications.

Citations

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